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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/790,943	WILSON ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007 and 31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11-13,16,17,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *16 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 7-8, 11-13, 16-17, and 20-21 are presented for examination

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submissions filed on 10/11/2007 and 10/31/2007 have been entered.

Applicants' arguments, filed 10/11/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments with respect to claims 1-4, 7-8, 11-13, 16-17, and 20-21 have been considered but are moot in view of the new ground(s) of rejection.

Priority

Acknowledgment is made of Applicants' claim for foreign priority based on an application filed in Great Britain on 9/3/2001. It is noted, however, that Applicants have not filed a certified copy of the GB0121285.1 application. Applicants are reminded that a certified copy of the GB0121285.1 application must be filed before any patent issuing from the instant application is granted. Please see 37 C.F.R. 1.55(a)(2).

The earliest effective U.S. filing date of the instant application for prior art purposes is **September 3, 2002**, the filing date of PCT/GB02/04025, of which the instant application is a continuation.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 10/31/2007. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7-8, 11-13, 16-17, and 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the abbreviation "DMXAA".

The first use of an abbreviation in the claims should be preceded by the full meaning of the abbreviation so as to clearly convey what is being claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-8, 11-13, 16-17, and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Davis** (WO 00/48591; Published 8/24/2000) (cited by Applicants in IDS filed 10/31/2007) in view of Applicants' disclosure at page 9, line 14 and page 12, lines 17-19.

The instant claims recite methods and compositions for treating solid cancerous tumors comprising administering DMXAA and gemcitabine. It is noted that the "comprising" language of the instant claims is open language that does not preclude the addition of other therapeutically active agents. Please see M.P.E.P. 2111.03.

Davis teaches methods of inhibiting the formation of new vasculature by angiogenesis comprising administering a combination of a vasculature damaging agent and an inhibitor of the formation or action of nitric oxide in mammalian systems (Abstract).

With respect to DMXAA as recited in claims 1-4, 7-8, 11-13, 16-17, and 20-21, Davis teaches that 5,6-dimethylxanthenone acetic acid (*i.e.*, DMXAA) is a chemical compound shown to have vascular damaging activity against the newly formed endothelium of solid tumors (page 1, lines 26-27) and is exemplified as an agent useful in the invention (page 3, line 31; page 4, line 31).

With respect to the treatment of solid tumors as recited in claims 1-4, Davis teaches that the method of the invention can be used to treat cancers, especially solid tumors (page 2, lines 21-22).

With respect to gemcitabine as recited in claims 1-4, 7-8, 11-13, 16-17, and 20-21, Davis teaches that the vasculature damaging agent/nitric oxide inhibitor combinations disclosed therein can be administered in combination with other treatments (page 6, lines 20-21). For the treatment of solid tumors, the combination may be administered in combination with other anti-

tumor agents (*id.* at lines 21-23). In this regard, antimetabolites, for example 5-fluorouracil and cytosine arabinoside, are taught to be suitable anti-tumor agents for use in combination with vasculature-damaging agents and nitric oxide inhibitors (*id.* at lines 25-26). At page 9, line 14 and page 12, lines 17-19 of the instant application, Applicants acknowledge that gemcitabine and 5-fluorouracil are suitable antimetabolites of use in combination with DMXAA, thus teaching their functional equivalence. Accordingly, the use of gemcitabine in combination with a vasculature-damaging and nitric oxide inhibitor as taught in Davis would have been *prima facie* obvious.

With respect to concomitantly and sequentially administering DMXAA and gemcitabine as recited in instant claims 3-4, Davis teaches that combination therapy may involve simultaneous or sequential application of the individual components of the treatment, thus motivating concomitant and sequential administration as instantly claimed (page 6, lines 30-32).

With respect to the compositions, pharmaceutical formulations, and kits recited in instant claims 7-8, 11, and 20-21, Davis teaches the use of a composition of the invention for the preparation of a medicament for the treatment of a disease involving active angiogenesis (page 7, lines 1-3; Claims 1-10).

With respect to pharmaceutically acceptable carriers and intravenous administration as recited in instant claims 11-13 and 16-17, Davis teaches compositions that may include pharmaceutically acceptable excipients and compositions adapted for intravenous administration (page 5, lines 22-23 and lines 30-32).

Accordingly, in the absence of a showing of unexpected results commensurate in scope with claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time

of the invention to combine a vasculature-damaging agent such as DMXAA, a nitric oxide inhibitor, and an antimetabolite such as gemcitabine for use in the treatment of solid tumors. The skilled artisan would have been motivated to do so because Davis teaches that nitric oxide inhibitors potentiate the activity of vasculature-damaging agents and that for the treatment of solid tumors, the vasculature-damaging agent and nitric oxide inhibitor may be combined with other anti-tumor agents. As such, one skilled in the art would have been imbued with at least a reasonable expectation that a combination of DMXAA (vasculature-damaging agent), a nitric oxide inhibitor, and gemcitabine (antimetabolite anti-tumor agent) would be an effective treatment for solid tumors.

As noted *supra*, the transitional term "comprising" as used in the instant claims is synonymous with "including" or "containing" and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. As such, the instant claims do not preclude the addition of an inhibitor of nitric oxide as taught by Davis.

Claims 1-4, 7-8, 11-13, 16-17 and 20-21 are again rejected under 35 U.S.C. § 103(a) as being unpatentable over **Siemann *et al.*** (Proceedings of the American Association for Cancer Research, 2000, vol. 41, page 525) and **Pruijn *et al.*** (Cancer Chemother. Pharmacol., 1997, col. 39, pages 541-546) in view of **Grindley *et al.*** (USP No. 5,464,826; Issued Nov. 7, 1995) (newly cited) and **van Moorsel *et al.*** (Biochemical Pharmacology, 1999, vol. 57, pages 407-415).

The instant claims are drawn to methods, compositions, and kits comprising DMXAA and gemcitabine. Dependent claims recite that the agents are in a potentiating ratio.

Siemann *et al.* teach that DMXAA enhances (*i.e.* potentiates) the efficacy of the chemotherapeutic agents cisplatin and cyclophosphamide in rodent (KHT sarcoma) and human (SKBR3 breast and OW1 ovarian carcinoma) tumor models. DMXAA (17.5 mg/kg) was shown to increase the tumor cell kill of cisplatin and cyclophosphamide by 10-500-fold over that seen with chemotherapy alone (Abstract). The reference thus demonstrates that DMXAA potentiates the antitumor effect of two traditional chemotherapeutic agents in a mammalian tumor model of breast and ovarian tumors.

Pruijn *et al.* also teach enhancing the antitumor activity of an anticancer agent, in this case melphalan, by co-administering melphalan with DMXAA (Abstract). DMXAA is well known in the art as an antitumor agent that inhibits tumor blood flow (page 541, right column, "Introduction"). DMXAA is also disclosed to enhance the antitumor effects of hypoxia-selective cytotoxins (*id.*). DMXAA was formulated in phosphate-buffered saline and melphalan was dissolved in 60% propylene glycol with 40% sodium citrate and both solutions were injected *i.p.* (page 542, left column, "Materials and Methods"). The reference thus motivates one skilled in the art to formulate the compositions recited in instant claims 7-8, 11-13, 16-17, and 20-21. Figure 1 (page 543) demonstrates that DMXAA and melphalan can be administered concomitantly or sequentially and in both cases DMXAA potentiates the effect of melphalan. The reference thus expressly suggests concomitant and sequential administration as recited in claims 3-4. The reference thus expressly suggests that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the alkylating agent caused by falling tumor blood flow (page 545, right column, last full paragraph). One skilled in the art would have been imbued with at least a

reasonable expectation that DMXAA would have this effect on any known anticancer agent, including the instantly claimed gemcitabine. The authors conclude that the study demonstrates the potential of DMXAA to "induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions (*id.*).

The primary and secondary references do not explicitly teach combining DMXAA with gemcitabine as recited in the instant claims.

Grindley *et al.* is provided as evidence that the instantly claimed gemcitabine was a compound known to be effective in treating cancer, including the instantly claimed solid tumors. In this regard, Grindley *et al.* teach a class of 2',2'-difluoronucleosides that can be used to treat neoplasms (Abstract). With respect to gemcitabine, this compound is exemplified at column 10, lines 7-8; Table 1; and claims 2, 4-5, and 7. With respect to solid tumors, Grindley *et al.* teach that the compounds of the invention can be used to treat tumors, both solid and non-solid type (col. 16, lines 13-15). Compositions and formulations as recited in claims 7-8, 11-13, 16-17, and 20-21 are disclosed at column 16, lines 20-63. Grindley *et al.* do not teach combining gemcitabine with other anticancer agents.

However, van Moorsel *et al.* disclose combination chemotherapy studies with gemcitabine and etoposide in non-small cell lung and ovarian cancer cell lines. These antineoplastic agents are known in the art to have clinical activity against various solid tumors (Abstract). Because gemcitabine and etoposide have different mechanisms of action, the drugs were combined and studied *in vitro*. Gemcitabine has clinical activity in several solid tumors, such as ovarian cancer, NSCLC, head and neck cancer, and pancreatic cancer (page 407). Gemcitabine becomes phosphorylated to its triphosphate and is subsequently incorporated into

DNA, followed by one or more deoxynucleotides after which DNA polymerization stops. Etoposide is a widely used anticancer agent that inhibits topoisomerase II (pages 407-408). Gemcitabine was solubilized in PBS for the experiments (page 408). The combined chemotherapy was shown to be synergistic in ovarian and NSCLC cells lines (Table 2). The reference thus motivates combining gemcitabine with other anticancer agents in the treatment of cancer and further demonstrates that such a combination could be synergistic in nature.

Thus, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer DMXAA in combination with gemcitabine as taught by Siemann *et al.* and Pruijn *et al.* in view of Grindley *et al.* and van Moorsel *et al.* One would have been motivated to do so because each of the therapeutics instantly claimed (DMXAA and gemcitabine) have been individually taught in the prior art to be successful at treating cancer, and further, Siemann *et al.* and Pruijn *et al.* explicitly teach combination therapy for the treatment of cancer using DMXAA and a second therapeutic agent. Further still, van Moorsel *et al.* teach combination therapy comprising gemcitabine and a second therapeutic agent. Accordingly, one of ordinary skill in the art would have been imbued with at least a reasonable expectation that gemcitabine and DMXAA in combination would be effective in treating solid tumors.

Moreover, the instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught

in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a *reasonable expectation of success* that by administering DMXAA in combination with gemcitabine as motivated by Siemann *et al.* and Pruijn *et al.* in view of Grindley *et al.* and van Moorsel *et al.*, one would achieve a method of treating cancer. While *In re Kerkoven* is limited to the mechanical arts, the holdings in this case are pertinent to the present claims because the idea of combining two known anticancer drugs to treat cancer flows logically from the individual drugs being taught to be useful in treating cancer. As such, one skilled in the art would reasonably expect the combination of drugs to also be effective in treating cancer. This is especially true in the present case where the prior art teaches that combinations of DMXAA or gemcitabine with other anticancer agents having different mechanisms of action are effective to treat cancer.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the present case, it is expressly recognized in the prior art that combining DMXAA or gemcitabine with other known anticancer agents would be expected to result in a composition useful for treating cancer.

Finally, it is clear from the prior art that DMXAA potentiates the antitumor effect of a number of anticancer agents (*e.g.* cisplatin, cyclophosphamide and melphalan) because of its mechanism of action (inhibiting tumor blood flow). As such, one skilled in the art would have

been imbued with at least a reasonable expectation that DMXAA combined with gemcitabine would be effective as an antitumor composition.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
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